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Preface to Hsp90

The heat-shock protein 90 (Hsp90) is more than a single protein. It is at the heart of a ubiquitous and conserved molecular machine with a large cohort of more or less constant parts. Hsp90, already present in prokaryotes, is essential and extremely abundant in eukaryotes. Indeed, its name is somewhat of a misnomer since it is relatively poorly induced by heat or other stresses above its very high basal levels. In addition to the nucleocytoplasmic versions, there are related isoforms in mitochondria, chloroplasts, and the endoplasmic reticulum. Functionally, the cytosolic Hsp90 machine intersects with a large number of cellular processes, and it has recently become a drug target for the treatment of cancer and other diseases. All of this has led to a massive explosion of the literature over the last years. As of December 2011, a PubMed search with Hsp90 as the keyword retrieves 6000 citations, and the combination "Hsp90 AND cancer" almost 2000. The core of the Hsp90 community may not be huge, but the fringes are enormous. This may not be a surprise for a molecular machine that has been estimated to handle up to 10% of all cellular proteins. In the jargon of the Hsp90 community, those are the clients (the substrates).

Although Hsp90 has regularly been the subject of reviews, including by several of the authors who contributed to this Special Issue, the field has become so vast that no single review can cover all aspects anymore. A collection of reviews in one place comes much closer to a comprehensive overview. This Special Issue is both for the diehard Hsp90 aficionados and for those looking for a serious jump-start. As an updated snapshot of the field, it nicely complements and expands the efforts of your guest editor to make information about the Hsp90 chaperone machine available through his web site (http://www.picard.ch). For the Hsp90 interactome, this includes the most recent addition of the online database Hsp90Int.db at the same web address. The Special Issue will also constitute a valuable companion for the biannual conference series on "the Hsp90 molecular chaperone machine" (see http://www.hsp90.org) that has been going on for almost ten years.

J. Johnson starts off with an overview of the Hsp90 family, its co-chaperones and functions, embedded in an evolutionary perspective. C. Prodromou discusses the intricate relationship between structure and function for the highly dynamic molecular machine composed of Hsp90 and co-chaperones. This review is complemented by that of J. Buchner and coauthors who focus on the intricate and highly dynamic multistep Hsp90 chaperone cycle with its transitions driven by ATP binding and hydrolysis and co-chaperone interactions. NMR spectroscopy as a tool to study the structure and function of this complex machinery in solution, as it works on clients as it were, takes center stage in the chapter by S. Rüdiger and coauthors. M. Mollapour and L. Neckers introduce the reader to yet another level of complexity by reviewing how a bewildering number of post-translational modifications control and fine-tune this molecular machine. S. D. Hartson and R. L. Matts compare the proteomic and genetic efforts that have been made to define the Hsp90 interactome, and more generally the Hsp90-dependent proteome, and present the synthesis in a highly useful form. F. J. Echtenkamp and B. C. Freeman reflect on the role that co-chaperones play, beyond regulating the Hsp90 ATPase, by expanding the "repertoire", the "zone of influence" of Hsp90 et al. One particular class of Hsp90 clients that are emerging are protein complexes, as presented by T. Makhnevych and W. A. Houry. M. A. Theodoraki and A. J. Caplan examine the connections between Hsp90 and the ubiquitin system in quality control of cytosolic proteins in physiological and pathological conditions. The next few chapters then address the biological role of the Hsp90 machine for a variety of organisms. For Y. Kadota and K. Shirasu, the biological system is plants, where Hsp90 in collaboration with a specific set of co-chaperones plays a particularly well-illustrated role in the response against pathogens. J. Frydman and coauthors emphasize the importance of Hsp90 as a host factor for viruses and explore the diversity of requirements. U. Tatu and coauthors point out for protozoan pathogens that their own Hsp90 is essential and thus a potentially important drug target. K. Richter and coauthors then take the reader on a tour of Hsp90 biology in mammalian metazoans, except for the mouse that is covered, with a particular emphasis on steroid physiology, in a chapter by E. R. Sanchez. Hsp90 even venturing outside of cells, its impact on wound healing and tumor cell invasion are reviewed by W. Li and coauthors. Speaking of cancer, the next two chapters thoroughly cover the current state of affairs. G. Chiosis and coauthors present the ongoing efforts to bring Hsp90 inhibitors to the clinic for the treatment of cancer and possibly even neurodegenerative diseases. L. Whitesell and N. U. Lin further discuss this theme and an intellectual framework for developing effective Hsp90-targeted chemotherapies. The two final chapters give credit to the fact that "Hsp90" is more than just "cytosolic Hsp90". D. C. Altieri and coauthors give an update on the mitochondrial isoform of Hsp90, Trap1, and highlight its potential as a drug target in cancer. Y. Argon and coauthors discuss Grp94, the isoform of the endoplasmic reticulum that a more limited but no less important set of proteins calls upon.

Despite everything that can be learned from this compendium, it will also make brutally clear that so many more discoveries are needed to answer key questions and harness all of this knowledge for personalized medicine. As a way of teasing the reader to stay tuned to the Hsp90 field, let me mention a few of the open questions and challenges. And note that most of them apply indiscriminately to all of the Hsp90 isoforms and locales. We still do not really understand how Hsp90 recognizes and binds its clients, nor how it does to them whatever it does to them. Indeed, what Hsp90 does to clients,

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or even only one client, in structural and biochemical terms, has yet to be worked out. There may be almost as many answers to these questions as there are clients, but there must at least be patterns. There are too many known co-chaperones, and probably a few more unknown ones, to be all present at the same time or even one after the other. How is this choreography used, regulated and what for? Moreover, co-chaperones are proteins in their own right, many of them moonlighting away from Hsp90 as well. The study of Hsp90 at the organismic level, from bacteria and viruses to mammals has considerably picked up steam in the last few years. Considering the numerous biochemical node functions of the Hsp90 complex, there is undoubtedly a lot more exciting biology in store. There is no question that in the Hsp90 field, we are all believers, believers in the therapeutic power of Hsp90 inhibitors to fight viral, fungal and protozoan infections, cancer, neurodegenerative and yet other diseases. But we have yet to understand why cancer cells are more sensitive to Hsp90 inhibitors, why inhibitors seem to work for some but not for other cancers, what exact treatment regimen needs to be applied or how Hsp90 inhibitors should be combined with other drugs. A lot of food for thought and challenges, not bad for a protein that started out in science as a simple band on a gel (of 90 kD).

Didier Picard is a professor of cell biology at the University of Geneva, Switzerland. He studied molecular biology as an undergraduate student at the University of Zurich, Switzerland. Working on transcriptional enhancers with Walter Schaffner, he obtained his PhD at the University of Zurich in 1985. As a postdoctoral fellow with Keith R. Yamamoto at the University of California, San Francisco, USA, he switched to studying the mechanism of hormonal regulation of steroid receptor activity. It is in this context that he began to work on the molecular chaperone Hsp90. After his appointment as a full professor at the University of Geneva in 1990, he was chair of the Department of Cell Biology for many years. In 2003, he was elected EMBO member. Since 2006, he has been the head of Biology of the Faculty of sciences. For his research, he has maintained his two-pronged interest in steroid receptors on the one hand and Hsp90 on the other. The latter led him to maintain a highly visited web site with Hsp90-related information and, in 2002, to initiate a series of biannual international meetings on the Hsp90 chaperone machine.

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